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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,606	03/28/2006	Jo Klaveness	PN0368	6864

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
07/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,606	KLAVENESS ET AL.	
	Examiner	Art Unit	
	MELISSA PERREIRA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-18,20,21 and 23-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18,20,21 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 5/26/09 has been entered.

Terminal Disclaimer

2. The terminal disclaimers filed on 9/12/07 disclaiming the terminal portion of any patent granted on this application have been accepted. The terminal disclaimers have been recorded.

Previous Claims and Rejections Status

3. Claims 15-18,20,21 and 23-25 are pending in the application. Claims 13 and 22 were cancelled and claim 25 was added in the amendment filed 5/26/09.

4. The rejection of claims 15-18,20, 21 and 23-25 under 35 U.S.C. 103(a) as being unpatentable over Maten et al. (*Gastroenterol.* **2002**, *122*, 406-414) in view of

Klaveness et al. (US 6,610,269B1) and further in view of Waggoner et al. (US 6,008,373) is maintained but modified to include newly added claim 25.

5. The rejection of claims 15-18, 20,21 and 23-25 under 35 U.S.C. 103(a) as being unpatentable over Weissleder et al. (*Nature Biotech.* **1999**, *17*, 375-378) in view of Klaveness et al. (US 6,610,269B1) and further in view of Waggoner et al. (US 6,008,373) is maintained but modified to include newly added claim 25.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 15-18,20,21 and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marten et al. (*Gastroenterol.* **2002**, *122*, 406-414) in view of Klaveness et al. (US 6,610,269B1) and further in view of Waggoner et al. (US 6,008,373).

8. Marten et al. (*Gastroenterol.* **2002**, *122*, 406-414) discloses cathepsin B sensing NIR fluorochrome probes comprising Cy5.5 (cyanine dye) containing cleavage sites, and a partially pegylated poly-L-lysine for imaging of the colon (p408, NIR fluorochrome probes; figure 2). The NIR fluorochrome probes are formulated for administration into mice (p408, NIR fluorochrome probes). Colonic adenomas can be visualized after injection of the NIRF probe into a mouse (figure 5) and colonic adenomatous polyps

ultimately lead to carcinoma formation and their detection has been shown to reduce the incidence of colorectal cancer. The probes are nonfluorescent in their native state but upon enzymatic cleavage the agent becomes fluorescent in the near-IR (figure 1; p412, paragraph 2). Maten et al. does not explicitly disclose that the NIR fluorochrome probes are pharmaceutical compositions comprising a pharmaceutically acceptable carrier which has a water solubility of at least 1mg/ml at pH 7.4 or that the contrast agents of the disclosure have a molecular weight of below 7,000 Daltons.

9. Klaveness et al. (US 6,610,269B1) discloses contrast agents of formula V-L-R where V is a vector moiety (i.e. peptide or non-peptide), L is a linker moiety (i.e. PEG) and R is a detectable reporter moiety/moieties (i.e. cyanine dye) for in vivo imaging (abstract; column 4, lines 10-20; column 5, lines 23-25; column 24, lines 56-58; column 28, lines 65+; column 42, line 40). The contrast agents of the disclosure are used for in vivo imaging of diseases associated with angiogenesis, such as colorectal cancer via administration with a physiologically acceptable carrier (column 3, line 27; column 4, line 53; column 56, lines 18-20). The linker moiety may contain 2-100 recurring units of ethylene oxide, have a molecular weight between 120 D to 20 kDa (column 33, line 1; column 36, lines 62-64) and also contain a biodegradable function which on breakdown can release the reporter from the vector (column 36, lines 14-18).

10. Waggoner et al. (US 6,008,373) discloses that low molecular weight fluorescent labeling complexes/probes containing cyanine dyes, linkers and proteins have enhanced cell penetrating capabilities (abstract; column 2, lines 38-43). The fluorescent labeling complexes/probes having greater penetration into cellular environments have

molecular weights of 500 to 10000 Daltons, and for a two fluorochrome complex, preferably in the range of 1000 to 2500 Daltons (column 3, lines 1-5; column 6, lines 15-22).

11. At the time of the invention it would have been obvious to one ordinarily skilled in the art to minimize the molecular weight of the fluorochrome probes of Marten et al. to 500 to 10000 Daltons (which includes below 7,000) or 1000 to 2500 Daltons (below 7,000) for a two fluorochrome complex by minimizing the linker molecular weight or the number of detectable reporter moieties to provide for probes having greater penetration into cellular environments. Also, the principles of cell penetration that apply in the imaging of isolated cells, such as that of Waggoner et al. would apply to imaging of cathepsin B done either *in vitro* or *in vivo*.

12. Klaveness et al. teaches that cyanine contrast agents, peptide-PEG-cyanine dye, may be formulated in a physiologically acceptable carrier to generate pharmaceutical agents for vivo imaging and therefore it would have been obvious to one skilled in the art to formulate the cyanine contrast agents of Marten et al. in a pharmaceutically acceptable carrier as both disclosures are drawn to in vivo imaging of the colon with cyanine contrast agents. Thus, the contrast agents/probes of the combined disclosures are useful for imaging the colon as they can provide for real time imaging that may have a significant impact on diagnosis of a very early stage of intestinal disease (Marten et al. p414, paragraph 4).

13. The contrast agents/probes of the instant claims do not provide any structural limitations over the prior art. Therefore, the contrast agents/probes of the combined

disclosures encompass those of the instant claims and are capable of the same functions and have the same properties, such as a water solubility of at least 1 mg/ml at pH 7.4. Therefore, if the prior art teaches the composition or renders the composition obvious, then the properties are also taught or rendered obvious by the prior art. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

14. Claims 15-18,20,21 and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissleder et al. (*Nature Biotech.* **1999**, *17*, 375-378) in view of Klaveness et al. (US 6,610,269B1) and further in view of Waggoner et al. (US 6,008,373).

15. Weissleder et al. (*Nature Biotech.* **1999**, *17*, 375-378) discloses NIRF probes for in vivo imaging comprising poly-L-lysine, MPEG and Cy5.5 (cyanine dye) (abstract; p375, paragraph 4). The NIRF probes of the disclosure are enzymatically activatable, thus producing fluorescence upon enzymatic cleavage (p375, paragraphs 2, 4 and 5). The NIRF probes were internalized into colon adenocarcinoma via uptake through fluid phase endocytosis thus indicating the feasibility of using these for the detection of primary tumors in the colon, such as colon cancer (p376, paragraph 1; p377, paragraph 1). Weissleder et al. does not explicitly disclose that the NIR fluorochrome probes are pharmaceutical compositions comprising a pharmaceutically acceptable carrier or that the contrast agents of the disclosure have a molecular weight of below 7,000 Daltons.

16. Klaveness et al. (US 6,610,269B1) discloses contrast agents of formula V-L-R where V is a vector moiety (i.e. peptide or non-peptide), L is a linker moiety (i.e. PEG) and R is a detectable reporter moiety/moieties (i.e. cyanine dye) for in vivo imaging as well as that stated above.

17. Waggoner et al. (US 6,008,373) discloses that low molecular weight fluorescent labeling complexes/probes containing cyanine dyes, linkers and proteins have enhanced cell penetrating capabilities (abstract; column 2, lines 38-43). The fluorescent labeling complexes/probes having greater penetration into cellular environments have molecular weights of 500 to 10000 Daltons, and for a two fluorochrome complex, preferably in the range of 1000 to 2500 Daltons (column 3, lines 1-5; column 6, lines 15-22).

18. At the time of the invention it would have been obvious to one ordinarily skilled in the art to minimize the molecular weight of the fluorochrome probes of Weissleder et al. to 500 to 10000 Daltons (which includes below 7,000) or 1000 to 2500 Daltons (below 7,000) for a two fluorochrome complex by minimizing the linker molecular weight or the number of detectable reporter moieties to provide for probes having greater penetration into cellular environments. Also, the principles of cell penetration that apply in the imaging of isolated cells, such as that of Waggoner et al. would apply to imaging of cathepsin B done either *in vitro* or *in vivo*.

19. Klaveness et al. teaches that cyanine contrast agents, peptide-PEG-cyanine dye, may be formulated in a physiologically acceptable carrier to generate pharmaceutical agents for vivo imaging and therefore it would have been obvious to one skilled in the

art to formulate the cyanine contrast agents of Weissleder et al. in a pharmaceutically acceptable carrier as both disclosures are drawn to in vivo imaging of the colon with cyanine contrast agents. Thus, the contrast agents/probes of the combined disclosures are advantageous for imaging the colon for the detection of the early stage tumors *in vivo* (Weissleder et al., abstract).

20. The contrast agents/probes of the instant claims do not provide any structural limitations over the prior art. Therefore, the contrast agents/probes of the combined disclosures encompass those of the instant claims and are capable of the same functions and have the same properties, such as a water solubility of at least 1 mg/ml at pH 7.4. Therefore, if the prior art teaches the composition or renders the composition obvious, then the properties are also taught or rendered obvious by the prior art. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

Response to Arguments

21. Applicant's arguments filed 5/26/09 have been fully considered but they are not persuasive.

22. Applicant asserts that the prior art references together do not disclose, teach or suggest a pharmaceutical composition for optical imaging for diagnosis of CRC. This is especially evident when the vector moiety weights, contrast agent weights, and water solubility of the contrast agents are combined and considered as a whole.

23. Klaveness et al. teaches that cyanine contrast agents, peptide-PEG-cyanine dye, may be formulated in a physiologically acceptable carrier to generate pharmaceutical agents for vivo imaging. Therefore it would have been obvious to one skilled in the art to formulate the cyanine contrast agents of Marten et al. or Weissleder et al. in a pharmaceutically acceptable carrier as all of the disclosures are drawn to in vivo imaging of the colon with cyanine contrast agents. Thus, the contrast agents/probes of the combined disclosures are advantageous for imaging the colon to provide for real time imaging that may have a significant impact on diagnosis of a very early stage of intestinal disease (Marten et al. p414, paragraph 4) and for the detection of the early stage tumors *in vivo* (Weissleder et al., abstract).

24. At the time of the invention it would have been obvious to one ordinarily skilled in the art to minimize the molecular weight of the fluorochrome probes of Marten et al. or Weissleder et al. to 500 to 10000 Daltons (which includes below 7,000) or 1000 to 2500 Daltons (below 7,000) for a two fluorochrome complex by minimizing the linker molecular weight or the number of detectable reporter moieties to provide for probes having greater penetration into cellular environments. Also, the contrast agents/probes of the instant claims do not provide any structural limitations over the prior art. Therefore, the contrast agents/probes of the combined disclosures encompass those of the instant claims and are capable of the same functions and have the same properties, such as a water solubility of at least 1 mg/ml at pH 7.4. Therefore, if the prior art teaches the composition or renders the composition obvious, then the properties are also taught or rendered obvious by the prior art. In re Spada, 911 F.2d 705, 709, 15

USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

/Melissa Perreira/
Examiner, Art Unit 1618